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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/874,166	06/04/2001	William Thomas Melvin	12489-003002/UMMC Ref: UM	8129

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/874,166	MELVIN ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/043,814.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 9/13/04. The amendment has been entered. Claims 27-35 are pending in the application and are examined herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-35 are finally rejected under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the

prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

It is noted that claim 27 has been amended to indicate that the method is drawn to a method for activating T cells in a subject by administering to the subject an amount of a cytochrome P450 CYP1B1 sequence effective to activate T cells that recognize a CYP1B1 epitope. As indicated in the response filed 9/13/04 (see p. 4), "to require that a CYP1B1 sequence (such as a CYP1B1 amino acid sequence or nucleic acid sequence) be administered to the subject..." (emphasis added). Therefore it is clear that the claim encompasses administering a nucleic acid sequence or an amino acid sequence to the subject. Administering a nucleic acid sequence is not enabled for the reasons indicated below. Since the previous claims did not explicitly claim administering a nucleic acid sequence, the amendment is necessitated by the amendment. The modified enablement rejection is set forth below. It is noted that the claims encompass activating T cells in a subject that has cancer (claims 31, 32) wherein the method results in a cell-mediated or humoral immune response against the cancer (claim 33). Since claim 27 is the independent claim which must, by definition, encompass all limitations set forth in the dependent claims, claim 27 (and as such, all pending claims) must encompass a method of activating a cell-mediated or humoral immune response against a cancer in a subject. Therefore, the claims encompass treating cancer by administering a tumor antigen sequence to a subject having cancer, which is not enabled for the reasons set forth in the previous office action, which is reiterated in the instant enablement rejection.

The nature of the invention

The claims are drawn to a method of activating T cells in a subject by administering a cytochrome P450 CYP1B1 sequence to the subject in an amount effective to activate T cells that recognize a CYP1B1 epitope, and includes stimulating an immune response against cancer cells. Therefore, the claims encompass cancer immunotherapy (e.g., treating cancer by administering a tumor antigen sequence).

The breadth of the claims

The claims are very broad. The broadest claims encompass stimulating T cells in a subject by administering a cytochrome P450 CYP1B1 sequence to the subject in an amount effective to activate T cells that recognize a CYP1B1 epitope. The claims also explicitly encompass administering any CYP1B1 sequence (such as SEQ ID NOS 1 or 2) that activates said human T cells.

The unpredictability of the art and the state of the prior art

The state of the art, including the post-filing art indicates that cancer immunotherapy and gene therapy (which is encompassed by the claims because the claims encompass administering a CYP1B1 nucleic acid sequence) are not methods that can be predictably performed.

For instance, with respect to administering a nucleic acid to a subject (i.e., gene therapy) the relevant art recognizes a number caveats and obstacles that must be overcome before the method can be predictably performed without an undue amount of additional experimentation.

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery that would provide efficient expression of genes encoding the therapeutic polypeptide (in this case the immunostimulatory amino acid sequence) sufficient to

result in the desired effect, in this case activating T cells. Currently, the state of the art of gene therapy is still in its infancy as the art is plagued by unpredictability. For instance, Crystal (Science, 1995; 270:404-409) teaches, "All of the human gene transfer studies have been plagued by inconsistent results, the basis of which are unclear", and sites specific examples including inconsistent results, the inconsistency of results in animal models and humans, vector production problems, and vector efficiency (see page 409, columns 1-2). Specifically, regarding the ideal gene therapy vector, Crystal teaches, "The vector should be specific for its target, not recognized by the immune system, stable and easy to reproduce... Finally it would express the gene (or genes) it requires for as long as long as required in an appropriately regulated fashion." (See p. 409, second column).

Verma et al. (Nature, 1997; Vol. 389) teaches, "there is still no single outcome that we can point to as a success story" (see pg. 239, col. 1; Gene Therapy Promises, Problems and Prospects). More recently, Walther and Stein (2000) reaffirms the obstacles to successful gene therapy by stating, "The hurdles to overcome in efficient gene therapy are successful gene transfer of the therapeutic genes, appropriate expression levels associated with sufficient duration of gene expression, and the specificity of gene transfer to achieve therapeutic effects in the patient." (See p. 267, under "Discussion"). Walther and Stein also indicate, "The majority of clinical trials using viral vectors for gene therapy in humans still lack a significant clinical success, defining the still existing barriers to achieving clinical benefits with gene therapy." (See pg.267, Discussion section).

To overcome the teachings in the art (with respect to administering a CYP1B1 nucleic acid sequence), the specification would need to supply direct, correlative guidance on how to

administer the CYP1B1 nucleic acid to a subject in such a way that the nucleic acid is delivered to an appropriate cell such that the nucleic acid expresses the CYP1B1 amino acid sequence in the cell, that the amino acid sequence is properly expressed (e.g., at an appropriate level for an appropriate duration of time and secreted from the cell at an effective amount) such that administration of the sequence effectively activated T cells in the subject such that method resulted in immune response against a cancer in the subject.

With respect to cancer immunotherapy, the relevant art recognizes a number caveats and obstacles that must be overcome before cancer immunotherapy methods can be can be predictably performed without an undue amount of additional experimentation.

For instance, Bodey et al. (2000; previously cited) teaches: "The cancer vaccine approach to therapy is based on the notion that the immune system could possibly mount a rejection strength response against the neoplastically transformed cell conglomerate. However, due to the low immunogenicity of tumor associated antigens, down regulation of MHC molecules, the lack of adequate co stimulatory molecule expression, secretion of immune inhibitory cytokines, etc., such expectation are rarely fulfilled...faulty antigen presentation which could result in tolerance induction to the antigens contained within the vaccine, and subsequent rapid tumor progression." (Page 2665, column one).

Gouttefangeas et al. (2000; previously cited) teaches,

> "As most cancer patients obviously do not mount efficient T cell responses against their tumors, the task is clear: immunotherapies must induce cancer-destroying T cells in patients. Although this goal appear straight forward, effective immunotherapy has remained elusive because of three major problems: first, for many tumors, no or not enough suitable antigens are known; second, no consensus exists for the best antigen

> formulation or the route of immunization; and third, tumors under immune attack tend to be selected for antigen loss variants." (See p. 491, first column).

Thus, Gouttefangeas indicates that patients that have tumors which express the tumor antigen do not mount an efficient immune response to these tumors. Therefore, administering a human tumor antigen to a human comprising a tumor that expresses the tumor antigen may not be sufficient to activate an immune response to the human tumor antigen. Furthermore, Gouttefangeas indicates that a single tumor antigen may not be sufficient to activate an effective immune response to the tumor; however, in the instant case, the specification has only described epitopes of a single tumor antigen, human CYP1B1. Finally, Gouttefangeas teaches that using immunotherapy for cancer treatment is unpredictable because the treatment can select for tumor cells that do not express the tumor antigen, thus rendering the treatment ineffective against the tumor cells that do not express the antigen.

Radoja et al. (Mol Med 2000; previously cited) teaches that cancer-induced defective cytotoxic T lymphocyte is probably another mechanism how tumor antigen escape immune surveillance. Specifically, Radoja teaches,

> "THE NOTION THAT A DEFICIT IN IMMUNE CELL FUNCTIONS PERMITS TUMOR GROWTH HAS RECEIVED EXPERIMENTAL SUPPORT WITH THE DISCOVERY OF SEVERAL DIFFERENT BIOCHEMICAL DEFECTS IN T LYMPHOCYTES THAT INFILTRATE CANCERS" (abstract). "ACCUMULATION OF CIRCULATING ANTITUMOR IMMUNOGLOBULIN G IN CANCER PATIENTS SHOW THAT THE PRIMING PHASE OF ANTITUMOR IMMUNE RESPONSE IS FUNCTIONAL DURING THE RELATIVELY SLOW PROCESS OF NASCENT TUMOR GROWTH...IN BOTH HUMAN CANCER PATIENTS AND RODENTS BEARING TUMORS OF DIFFERENT HISTOLOGIC ORIGIN, SYSTEMIC IMMUNITY IS NOT PROFOUNDLY SUPPRESSED..." "HOWEVER, INHIBITION OF A SPECIFIC ANTITUMOR IMMUNE RESPONSE HAS BEEN OBSERVED FREQUENTLY. A VARIETY OF MECHANISM HAVE BEEN PROPOSED TO ACCOUNT FOR DEFECTIVE ANTITUMOR IMMUNE RESPONSE, INCLUDING: SECRETION OF SUPPRESSIVE FACTORS IN THE TUMOR MICROENVIRONMENT, THE LACK OF EXPRESSION OF COSTIMULATORY SIGNALS ON TUMOR CELLS, INDUCTION OF REGULATORY T CELLS

> HAVING A SUPPRESSIVE PHENOTYPE, LOSS OF ANTIGEN PRESENTATION FUNCTION IN THE TUMOR, LOSS OF EXPRESSION OF HLA CLASS I ANTIGEN PRESENTING MOLECULES IN TUMORS, TUMOR-INDUCED T-CELL SIGNALING DEFECTS, LOSS OF TUMOR ANTIGEN EXPRESSION, IMMUNOLOGICAL IGNORANCE AND, SINCE MANY TUMOR ANTIGENS ARE EITHER UNMODIFIED SELF OR EPITOPES CLOSELY RELATED TO SELF, THE REDUCTION OF THE REPERTOIRE OF POTENTIAL HIGH AFFINITY ANTITUMOR T-CELL CLONES DURING T-CELL MATURATION IN THE THYMUS" (Introduction).

Thus, it is evident that the skilled artisan, while acknowledging the significant potential of immunotherapy for cancer, still recognizes that such therapy is neither routine nor wholly accepted. Furthermore, significant development and further guidance is necessary for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for the instant methods.

In order to enable the instant claims in light of the state of the relevant art, the applicant must provide guidance/working examples to demonstrate that the CYP1B1 epitopes are highly immunogenic and could provoke a useful immune response without the problems in the cited references or must provide ways to overcome the cited difficulties.

Working Examples and Guidance in the Specification

The specification does not have any working examples that indicate that a CYP1B1 sequence (including a CYP1B1 nucleic acid sequence and a CYP1B1 amino acid sequence comprising SEQ ID NO:1 or SEQ ID NO:2) can be used to: (1) activate T cells in a subject; and/or, (2) stimulate an immune response against a cancer in a subject. The only examples provided indicate that the human CYP1B1 epitopes disclosed (specifically, the amino acid sequences consisting of SEQ ID NO:1 and SEQ ID NO: 2) can be used to raise antibodies against the epitopes in mice. As indicated above activating T cells in a subject and stimulating

an immune response against a cancer using a tumor antigen epitope is not a matter of routine experimentation.

Quantity of Experimentation

Considering the breadth of the claims, and the unpredictability of gene therapy and cancer immunotherapy recognized in the art, additional experimentation is required in order for one of skill in the art to be able to practice the claimed invention. Considering the lack of working examples or guidance in the specification and also considering the teachings of the relevant art that the required experimentation is not routine, the amount of additional experimentation required is deemed to be undue.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of gene therapy and cancer immunotherapy recognized in the art, the breadth of the claims, the lack of working examples and guidance in the specification, and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed invention is undue.

Response to Arguments

Applicant's arguments filed 9/13/04 have been fully considered but they are not persuasive. Applicants assert that the independent claim has been amended to a method of activating T cells in a subject by administering a cytochrome P450 CYP1B1 sequence effective to activate T cells that recognize CYP1B1 epitope. Furthermore, applicants argue,

"As detailed in the working examples contained in the application as filed, the currently claimed invention is based, at least in part, upon applicants' discovery that CYP1B1 is expressed in a wide range of tumors but not in the normal tissues that were tested (see specification at page 2, lines 30-31 and Table 1 on page 16). As a result of this marked preferential expression of CYP1B1 in tumors, the specification teaches that CYP1B1 sequences can be used to immunize a subject, thereby resulting in activated T cells that recognize a CYP1B1 epitope and mediate an immune response against a CYPlBl-expressing tumor (see specification at page 4, lines 20-24). Because of the applicants' experimental findings clearly showing that CYP1B1 is expressed in many types of cancers, but not expressed in those normal tissues studied, the person of ordinary skill in the art at the time of filing of the present application would have reasonably expected that CYP1B1sequences could be used to generate an effective immune response against CYP1B1-expressing tumor cells. With respect to the Examiner's comments regarding the Wands factors, the claims have been amended by the present response to require the administration of a CYP1B1 sequence that activates T cells that recognize a CYP1B1 epitope ('breadth of the claims'). The amended claims thus do not encompass the use of 'any compound' that can activate human T cells. In addition, the striking experimental findings (contained in the application) of tumor specific expression of CYP1B1 would have caused the skilled artisan to reasonably expect that CYP1B1 could be used effectively as the target of a cancer immunotherapeutic composition ('working examples and guidance in the specification'). As a result of these teachings, and without the need for a working example describing the treatment of a subject with a CYP1B1 sequence, the person of ordinary skill in the art would have been able to carry out the claimed methods without undue experimentation and with a reasonable expectation of success." (See p. 7 of the response filed 9/13/04).

In response, it is acknowledged that the specification discloses that CYP1B1 is expressed in a wide range of tumor but not in the normal tissue that was tested. It is also acknowledged that the specification indicates that the CYP1B1 sequences can be used to stimulate an immune response against a cancer in a subject. It is also acknowledged that the claims have been amended such that the claims no longer encompass administering "any compound" to the subject. In response the written description has been withdrawn. (p. 4, lines 20-24). However, considering that the prior art indicates that the claimed method is unpredictable (for the reasons indicated herein), it is not sufficient that the specification merely discloses that CYP1B1 is a tumor-specific antigen. As such, applicants have not overcome the caveats and problems recognized in the relevant prior art. Therefore, the rejection is not withdrawn.

It is noted that a showing that the administration of CYP1B1 sequences to a subject (as indicated in the claims) could activate T cells and stimulate an immune response against cancer cells in a subject would overcome this rejection.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon Eric Angell, Ph.D.
Art Unit 1635

DAVE T. NGUYEN
PRIMARY EXAMINER